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(54) Title: APOPTOSIS MODULATORS THAT INTERACT WITH THE HUNTINGTON'S DISEASE GENE

(57) Abstract

A family of proteins, including a specific human protein designated as HIP1, has been identified that interact differently with the gene product of a normal (16 CAG repeat) and an expanded (>44 CAG repeat) HD gene. Expression of the HIP1 protein was found to be enriched in the brain. Analysis of the sequence of the HIP1 protein indicated that it includes a death effector domain (DED), suggesting an apoptotic function. Thus, it appears that a normal function of Huntingtin may be to bind HIP1 and related apoptosis modulators, reducing its effectiveness in stimulating cell death. Since expanded huntingtin performs this function less well, there is an increase in HIP1–modulated cell death in individuals with an expanded repeat in the HD gene. This understanding of the likely role of huntingtin and HIP1 or related proteins (collectively "HIP–apoptosis modulating proteins") in the pathology of Huntington's disease offers several possibilities for therapy. First, because the function of huntingtin apparently depends at least in part on the ability to interact with HIP–apoptosis modulating proteins, added expression (e.g., via gene therapy) of normal (non–expanded) huntingtin or of the HIP–binding region of huntingtin should provide a therapeutic benefit. Other DED–interacting peptides could also be used to mask and reduce the interaction of HIP–apoptosis modulating proteins with the death signaling complex. Alternatively, a mutant form of HIP–protein from which the DED has been deleted might be introduced, for example using gene therapy techniques. Because HIP–apoptosis modulating proteins have been shown to self–associate, a protein with a deleted DED may compete with endogenous HIP–protein in the formation of these associations, thereby reducing the amount of apoptotically–active HIP–protein.